AMENDMENTS TO THE DRAWINGS:

Please replace Figure 9 in the above-captioned application with the attached replacement Figure 9, labeled "Replacement Sheet," in compliance with 37 C.F.R. §1.84. A marked-up copy of the amended figure also is attached, labeled "Hand Annotated Drawings," on which the amendments are indicated in red ink.

Attachments following the last page of this Amendment:

Replacement Sheet (1 page)

Hand Annotated Drawings Showing Changes (1 page)

REMARKS

A check for the fee for a three month extension of time accompanies this response. Any fees that may be due in connection with this application throughout its pendency may be charged to Deposit Account No. 06-1050.

Claims 1, 5-9, 16-19, 21-23, 40, 43, 44, 46-74, 137, 139-144, 279, 306-308, 315, 316 and 332-347 are pending in the application. Claims 8, 9, 46-74, 140, 142-144, 279 and 306, which withdrawn from consideration as being drawn to non-elected subject matter, are retained for possible rejoinder upon allowance of a generic/linking claim. Claims1, 6, 7, 307, 341, 342 and 344 are amended for clarity and consistency, claim 138 is cancelled without prejudice or disclaimer, and claims 346 and 347 are added. No new matter is added.

An unexecuted DECLARATION under 37 C.F.R. §1.132 of Dr. Manuel Vega is filed herewith. An executed copy of the DECLARATION will be filed upon receipt.

A supplemental Information Disclosure Statement is mailed via Express Mail under separate cover on the same day herewith.

IN THE SPECIFICATION

Amendments to the specification correct minor typographical and spelling errors to produce grammatical clarity. For example, amendment to the paragraph beginning at page 10, line 26, seeks to correct an inadvertent error in referencing of a PDB code by deleting the referenced PDB code 1ITF in the Figure legend for Figure 7(B). As stated in the Figure legend, Figure 7(B) depicts a side view ribbon representation of IFNα-2b structure. The PDB code 1ITF is the PDB code for the IFNα-2a structure. Hence, the amendment herein seeks to correct this error by omitting the reference to the incorrect PDB code. Basis for the amendment can be found, for example, in the specification as originally filed in the paragraph beginning at page 10, line 18, where the PDB code 1ITF is assigned to the IFNα-2a NMR structure.

In addition, amendments to the paragraphs beginning at page 54, line 24; page 137, line 8; and page 137, line 33, correct inadvertent errors in referencing of figure numbers. Basis for these amendments can be found in the figures as originally filed and in the BRIEF DESCRIPTIONS OF THE FIGURES section of the specification as originally filed beginning at page 7, line 2. For example, amendments to the paragraphs beginning at page 54, line 24, and page 137, line 8, correct references to Figure 6A (FIG6A) and/or Figure 6B (FIG6B) by replacing them with references to Figure 1A (FIG1A) and/ or Figure 1B (FIG1B), respectively. On page 54, lines 24-26, the specification references FIG6A in

describing residues in a target protein potentially targeted for proteolysis. Further, in the paragraph beginning at page 137, line 8, the specification also references FIG6A in describing target amino acids potentially sensitive to protease digestion. The reference to FIG6A in both instances is incorrect since FIG6A as originally filed shows the characterization of an IFNα-2b variant treated with α-chymotrypsin and not amino acid residues potentially targeted for proteolysis. The amendment presented herein seeks to correct the references from FIG6A to FIG1A since FIG1A correctly displays the residues in IFNα-2b targeted by a mixture of proteases. Basis for the amendment can be found in the legend for FIG1A as shown on page 7, line 2. In addition, in the paragraph beginning on page 37, line 8, the specification references FIG6B in describing the 3-dimensional structure of the IFNα-2b molecule. The reference to FIG6B is incorrect since FIG6B as originally filed shows the characterization of an IFNα-2b variant treated with a mixture of proteases and not the 3-dimensional structure of the IFNα-2b molecule. The amendment presented herein seeks to correct the reference from FIG6B to FIG1B since FIG1B correctly displays the structure of IFNα-2b. Basis for the amendment can be found in the legend for FIG1B as shown on page 7, line 7.

Similarly, amendments to the paragraph beginning at page 137, line 33, correct references to Figure 7 (FIG7) and Figure 8 (FIG8) by replacing them with references to Figure 2 (FIG2) and Figure 3 (FIG3), respectively. On page 137, lines 33-34 and page 138, lines 1-3, the specification refers to FIG7 in describing a PAM250 matrix, and to FIG8 in using the PAM250 matrix to choose amino acid residues for substitution. The references to FIG7 and FIG8 are incorrect since FIG7 and FIG8 as originally filed depict NMR structures of IFNα-2b and overlapping NMR structures with other cytokines, respectively, whereas, FIG2 and FIG3 as originally filed correctly depict the PAM250 matrix and the PAM250 amino acid substitution analysis. Hence, the amendment presented herein seeks to correct the references to FIG2 and FIG3. Basis for the amendments can be found in the legends for FIG2 and FIG3 as shown on page 7, lines 11-20.

Amendment to the paragraph beginning at page 138, line 11, seeks to correct the amino acid listed at position 23 as Lysine (K) by replacing it with an Arginine (R) residue, as depicted in the mature wild-type sequence of IFN-α2b listed in SEQ ID NO: 1 of the Sequence Listing. Basis for the amendment can be found, for example, within SEQ ID NO: 1 of the Sequence Listing as originally filed. SEQ ID NO: 1 is also described in the specification at page 5, lines 30-31; page 61, lines 8-9; page 82, line 5; and page 140, lines

31-33 as interferon alpha-2b (IFN-α2b). As further support for the amendment, the amino acid Arginine (R) is listed as the wild-type amino acid for position 23 in Figure 1A as originally filed.

Amendment to the paragraph beginning at page 139, line 25, seeks to correct the inadvertent error in reference of IFNα-2b by replacing it with IFNα-2a. In lines 25-26, the specification incorrectly identifies IFNα-2b as having the PDB code 1ITF, where 1ITF is the PDB code for IFNα-2a, not IFNα-2b. Basis for the amendment can be found, for example, in the specification as originally filed in the paragraph beginning at page 7, lines 7-8, where PDB code 1ITF is provided for IFNα-2a.

No new matter has been added to the specification.

IN THE FIGURES

In accordance with 37 C.F.R. §1.121(d), amendments to the drawing of Figure 9 (FIG. 9) of the above-referenced application is respectfully requested. Attached herewith is a replacement drawing of FIG. 9, labeled "Replacement Sheet," in compliance with 37 C.F.R. §1.84. A marked-up copy of the drawing, labeled "Annotated Marked-Up Drawings," also is enclosed herewith; the amendments to the FIG. 9 are indicated in red ink. Amendments to the Figures include amendments to FIG. 9 to correct the amino acid sequence of IFN-α2b depicted in FIG. 9. The sequence of IFN-α2b depicted in FIG. 9 inadvertently has one incorrect amino acid listed at position 23 with respect to the mature IFN-α2b amino acid sequence. FIG. 9 is amended herein to correct this inadvertent error by amending the sequence to replace the Lysine (K) residue at position 23 with an Arginine (R) residue, as depicted in the mature wild-type sequence of IFN-α2b listed in SEQ ID NO: 1 of the Sequence Listing. Basis for this amendment can be found within SEQ ID NO: 1 of the Sequence Listing as originally filed. SEQ ID NO: 1 is also described in the specification at page 5, lines 30-31; page 61, lines 8-9; page 82, line 5; and page 140, lines 31-33 as interferon alpha-2b (IFN-α2b). As further support for the amendment, the amino acid Arginine (R) is listed as the wild-type amino acid for position 23 in Figure 1A as originally filed. No new matter has been added to the Figures.

Preliminary Remarks

Interferon alpha family

The interferon alpha (IFNα) family of cytokines contains numerous species, including those designated IFNα1, α2, α4, α5, α6, α7, α8, α10, α14, α16, α17 and α21, which are encoded by different genes. Each gene include multiple alleles. The nomenclature to

describe the IFNα family varies in different publications. Table 1 in Testa et al. (US Patent No. 5,676,942) describes the correspondence of IFN alpha polypeptide nomenclature.

In particular, interferon α2a, interferon α2b and interferon α2c are encoded by alleles of the gene encoding interferon α2; each differing in only a single amino acid from the other. The interferons encoded by the different genes also are highly conserved. A sequence alignment showing the sequences of a variety of interferon alpha polypeptides, whose sequences are included in the instant application, is attached to this response. In the alignment, the SEQ ID NOS are specified, with the species of interferon indicated in the adjacent parentheses. The alignment shows that the IFNα species exhibit a high degree of sequence identity. For example, in the Sequence Alignment, IFNα-2b is highlighted in green, and corresponding residues in other IFNα species that are different are highlighted in yellow.

Election of species

Applicant acknowledges the finality of the election of species as to an IFN-α2b containing replacement of E by Q at position 41. It respectfully is submitted, however, that there is an error in identification of claims to be withdrawn. Claims 279 designated as withdrawn reads on the elected species. Also, it appears that the Examiner has failed to identify linking claims.

In addition, while Applicant has elected a modified interferon α-2b, it respectfully is submitted that examination of interferon α-2a and interferon α-2c, which are allelic variants of the same gene (designated αA, see, *e.g.*, Testa, col. 1 Table 1) that each differ in only one amino acid (a K to R or R to H; see attached sequence alignment) from interferon α-2b, would not be an undue burden. Surely the Patent Office does not contend that a proteins encoded by each allele of a gene require a separate patent. Furthermore, it would be unfair and unduly limiting to limit the claims to a single allele of a known gene. Those of skill in the art readily avoid infringing such claims by following the teachings in the specification employing a protein encoding an alternative allele.

Withdrawn Subject Matter

The Examiner indicates that claims 8, 9, 46-74, 140, 142-144, 279 and 306 are withdrawn as being directed to non-elected species. Applicant respectfully submits that this is an error at least with respect to claim 279, which reads on the elected species (SEQ ID No. 87) which is E41Q in interferon alpha-2b (SEQ ID No. 1) . Claim 279 recites:

> An interferon alpha cytokine of claim 1 selected from among modified cytokines comprising a sequence of amino acids set forth in any of

> SEQ ID NOS: 2-181, 978-988 or 1303 or an interferon alpha structural homolog thereof.

Since the elected species is set forth in SEQ ID No. 87, which is SEQ ID No. with the E41Q change, claim 279 encompasses the elected species. Claim 279 reads on the elected species because SEQ ID NO:87 is the sequence of amino acids for an interferon-alpha 2b having replacement of E by Q at position 41. Thus, claim 279 is retained herein

Linking Claims

The remaining claims 8, 9, 46-74, 142-144 and 306 are indicated as withdrawn for being directed to non-elected subject matter, which do not encompass the elected species. These claims should be rejoined pending allowance of a genus claim. As discussed below, claims 1, 40 and 332-340 are generic (i.e. link) all of the species and withdrawn claims. Claims 1, 21, 40, 43, 44 and 332-340 are generic to the withdrawn subject matter of claims 46-74 and 142-144. Claims 1, 5, 16-22, 40 139-141 and 332-340 are generic to the withdrawn subject matter of claim 306. As discussed below, generic claims are linking claims.

The, Applicant respectfully requests correction of the identification of the genus/linking claims as to the withdrawn claims 46-74, 142-144 and 306, and as to claims encompassing nonelected species.

Contrary to the Examiner's statement, Applicant respectfully submits that genus claims are linking claims. See MPEP § 809, which defines one type of linking claim as a genus claim linking species claims:

> Linking claims and the inventions they link together are usually either all directed to products or all directed to processes (i.e., a product claim linking properly divisible product inventions, or a process claim linking properly divisible process inventions). The most common types of linking claims which, if allowable, act to prevent restriction between inventions that can otherwise be shown to be divisible, are
>
> (A) genus claims linking species claims; and
>
> (B) subcombination claims linking plural combinations.

Pursuant to MPEP 809, the linking claims should be examined with the elected group. If a linking claims is deemed allowable, the restriction requirement/election requirement as to all claims/groups linked thereby must be withdrawn and all claims directed to nonelected subject matter that depends from or includes all the limitations of the linking claims must be rejoined. Hence, for example, if any of claims 1, 40 and 332-340 is deemed allowable, all claims should be rejoined. If any of claims 21, 43 and 44 is deemed allowable, claims 46-74 and

142-144 should be rejoined. If any of claims, 5, 16-20, 22, 40, and 139-141 is deemed allowable, claim 306 should be rejoined.

I. THE REJECTION OF CLAIMS 1, 5, 6, 16, 18, 19, 21-22, 43, 44, 307, 308, 315-316 AND 332-339 UNDER 35 U.S.C. §101

Claims 1, 5, 6, 16, 18, 19, 21-22, 43, 44, 307, 308, 315-316 and 332-339 are rejected under 35 U.S.C. §101 for allegedly being directed to non-statutory subject matter in view of Testa et al. (U.S. Patent No. 5,676,942). The Examiner alleges that Testa *et al.* discloses mixtures of natural IFN-α polypeptide, where the components of the mixture are IFN alpha 2b variants containing the mutation M16I, and thus discloses a mutant conferring increased resistance to proteolysis and all of the biochemical and biological properties of the mutants as claimed in the instant application. The Examiner appears to be saying that an interferon alpha 2b variant exists in nature, and, hence the rejected claims read on nature. This rejection respectfully is traversed.

It respectfully is submitted that the Examiner's premise is incorrect. Testa *et al.* shows peaks 2-6, which contain mixtures of interferon alpha species, contain an I at position 16. Testa *et al.* also states that peaks IFNα2b and 2c were found in peaks 1.1 and 1.2, all other IFNα species (IFN-α4a, α4b, α7a, α7b, α8a, α8b, α8c, α10a, α16, α17a, α17b, α17c, α17d, α21a and α21b) were found in the other peaks. Hence peaks 2-6, which include an I at position 16, do not contain IFN α2b (see, also Table 11, which describes the species of interferon-α in each of the peaks). As discussed above (see also, the attached alignment), none of IFN-α4a, α4b, α7a, α7b, α8a, α8b, α8c, α10a, α16, α17a, α17b, α17c, α17d, α21a and α21b is a variant of IFN-α2b nor IFN-α2c, or IFN-α2a. Thus, Testa does not disclose any IFN-α2b variants that include an I at position 16.

Furthermore, as drafted, none of the species encompassed in claim 1 can read on nature. Claim 1 (prior to amendment herein) recites:

> An interferon alpha cytokine, comprising one or more amino acid replacements in its sequence of amino acids, whereby the interferon alpha cytokine exhibits increased resistance to proteolysis compared to the unmodified interferon alpha cytokine that does not comprise the one or more amino acid replacements.

Hence claim 1 has two requirements for any interferon alpha: first, the interferon must have one or more replacement so that it exhibits increased resistance to proteolysis; and second, that the increased resistance is compared to the unmodified interferon alpha cytokine. Thus, an unmodified interferon α, such as any of IFN-α4a, α4b, α7a, α7b, α8a, α8b, α8c, α10a,

α16, α17a, α17b, α17c, α17d, α21a and α21b, which has an I at position 16, does **not** hjave an amino acid replacement, does **not** have increased resistance compared to the unmodified interferon alpha cytokine.

With respect to claims, such as claims 6, 307 and 308, which recite M16I as a possible replacement, these claims recite that the modification is in an interferon α-2a, α-2b, α-2c. Hence these claims do not read on of unmodified IFN-α4a, α4b, α7a, α7b, α8a, α8b, α8c, α10a, α16, α17a, α17b, α17c, α17d, α21a and α21b. Therefore, none of the claims read on an interferon alpha that exists in nature as evidenced by Testa *et al.*

Finally, to ensure that the claims to not read on any as-yet-to-be identified interferon alpha that exists in nature in an impure state, claim 1 is amended to recite that the interferon alpha is isolated.

II. THE REJECTION OF CLAIMS 1, 5, 6, 16-18, 19, 21-22, 40, 43, 44, 139, 141, 307, 308, 315-316, 332-340 AND 343 UNDER 35 U.S.C. §102

Claims 1, 5, 6, 16-18, 19, 21-22, 40, 43, 44, 139, 141, 307, 308, 315-316, 332-340 and 343 are rejected under 35 U.S.C. §102 for allegedly being anticipated by Testa *et al.* (U.S. Patent No. 5,676,942). The Examiner alleges that Testa *et al.* discloses mixtures of natural human interferon alpha species and subunits, and urges that peaks 2-6 harbor IFN alpha 2b variants containing the mutation M16I as instantly claimed, thereby conferring the mutant increased protease resistance and all the biochemical and biological properties of the mutants as claimed in the instant application. The Examiner urges that the conditions and limitations of each of the rejected claims is anticipated by Testa *et al.* This rejection respectfully is traversed.

Relevant law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention

as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

The Rejected Claims

Independent claim 1 recites:

> An isolated interferon alpha cytokine, comprising **one or more amino acid replacements in its sequence of amino acids**, whereby the interferon alpha cytokine exhibits increased resistance to proteolysis *compared to the unmodified interferon alpha cytokine that does not comprise the one or more amino acid replacements.*

Each of claims 332-340 are dependent on claim 1 and recite particulars of the interferon alpha cytokine.

Claims 5 is dependent on claim 1 and specifies that the **unmodified interferon alpha is IFNα-2b, IFN-α2a, IFN-α2c** or a consensus interferon set forth in SEQ ID NO:32. Claim 5 recites:

> The interferon alpha cytokine of claim 1, wherein the unmodified interferon alpha cytokine is selected from among an interferon α-2b (IFNα-2b), an interferon α-2a (IFNα-2a), an interferon α-2c (IFNα-2c), and an interferon having the sequence set forth in SEQ ID NO: 232.

Each of claims 16-18, 19, 139, 141, are dependent on claim 5 and recite particulars of the modified interferon alpha.

Claims 6, 307 and 308 are dependent on claim 1 and specify particular amino acid replacements in an **IFNα2a, IFN-α2b or IFN-α2c** that confer protease resistance, including replacement of M by I at position 16. For example, claim 6 recites:

> An interferon alpha cytokine of claim 1, **that is an IFNα-2b or an IFNα-2a or an IFNα-2C** selected from among proteins comprising one or more single amino acid replacements corresponding to the replacement in SEQ ID NOS: 1, 182 or 185 of: ... M by I at position 16; ...,
>
> wherein residue 1 corresponds to residue 1 of the mature IFNα-2b or IFNα-2a cytokine set forth in SEQ ID NOS:1 or 182. [portions of claim deleted for ease of argument herein only]

Claims 315 and 316 are dependent on claim 308 and recite particulars of the activity of the interferon alpha cytokine.

Claim 21 is dependent on claim 1 and specifies that the modified interferon alpha cytokines has **two** or more amino acid replacements, and claim 22, dependent on claim 21, specifies the interferon alpha cytokine is a modified IFNα2b cytokine.

Claim 43 specifies that the interferon alpha is a structural homolog of IFNα-2b, and contains one or more amino acid replacements at positions corresponding to positions in

IFNα-2b, IFNα-2a, IFNα-2c or a consensus interferon alpha. Claim 44 is dependent on claim 43 and specifies that the modified interferon alpha structural homolog has increased protease resistance compared to its unmodified cytokine counterpart. Claim 43 recites:

> An interferon alpha cytokine of claim 1 that is a structural homolog of an IFNα-2b, comprising one or more amino acid replacements in the cytokine structural homolog at positions corresponding to the 3-dimensional-structurally-similar modified positions within the 3-D structure of a modified IFNα-2b, IFNα-2a, IFNα-2c or an interferon of SEQ ID NO: 232.

Claim 40 is directed to a pharmaceutical composition containing an interferon alpha cytokine of claim 1. Claim 343 specifies that the pharmaceutical composition is formulated for oral administration.

Hence, as discussed above, with respect to the rejection under 35 U.S.C. §101, all claims have at least two requirements for any interferon alpha: first, the interferon alpha must have one or more amino acid replacement so that it exhibits increased resistance to proteolysis; and second, that the increased resistance **is compared to the unmodified** interferon alpha cytokine. In addition, dependent claims, specifically recite that the modification is in an interferon alpha 2a, -2b, 2c or consensus sequence thereof (SEQ ID. No. 232).

Thus, the claims specify that the interferon alpha cytokine is modified by amino acid replacement(s), and that the modified interferon alpha exhibits increased protease resistance compared to the unmodified cytokine not containing the replacement(s). Claims 5 specifies that the unmodified interferon alpha is an IFN-α2a, IFN-α2b, IFN-α2c or a consensus interferon alpha and claims 6, 307 and 308 are directed to modified IFN-α2a, IFN-α2b, IFN-α2c containing specified amino acid replacements, such as M16I, in an unmodified interferon alpha cytokine that is an IFN-α2a, IFN-α2b, IFN-α2c. Claim 43 specifies that the interferon alpha cytokine is a *structural homolog* of an IFNα-2b containing replacements at positions corresponding to positions in a modified IFN-α2b, IFN-α2a, IFN-α2c or consensus interferon based on the 3-D structures.

Differences between the disclosure of U.S. Patent NO. 5,676,942 and the rejected claims

Testa et al. describes the isolation of **mixtures** of IFN-α species from IFNαn3a, which is a mixture of IFN-α species derived from leukocytes, using HPLC methods to separate the IFN-α species into seven peak preparations. N-terminal amino acid sequencing to determine the amino acid sequence of each of the RP-HPLC peaks showed that each of the interferon preparations contained multiple IFN-α sequences, except for peak 3 containing

IFNα10a. IFNα2b and 2c were found in peaks 1.1 and 1.2, all other IFNα species (IFN-α4a, α4b, α7a, α7b, α8a, α8b, α8c, α10a, α16, α17a, α17b, α17c, α17d, α21a and α21b) were found in the other peaks. Sequencing of peaks 2, 3, 4, 5 and 6 showed that all species within those fraction peaks had an isoleucine at position 16, while peaks 1.1 and 1.2 had a methionine. Testa et al. also discloses testing the anti-viral activities, as assessed by retroviral activities against Human Immunodeficiency Virus 1 (HIV-1), of the separated peaks, and disclose that each of peaks 2-6 have a greater anti-viral activity than peak 1 (combination of peaks 1.1 and peaks 1.2) containing IFN-α2. Hence, Testa et al. discloses naturally occurring compositions of IFN-α species from any one or more of IFN-α4a, α4b, α7a, α7b, α8a, α8b, α8c, α10a, α16, α17a, α17b, α17c, α17d, α21a and α21b that exhibit high antiviral potency. The compositions disclosed in Testa et al. do **not** contain IFN-α2, nor variants of IFN-α2.

It is noted that these species correspond to the *structural homologs* of interferon alpha disclosed in the instant application, albeit some using a different nomenclature (see, *e.g.*, Table 1 of Testa *et al.*). For example, IFNα17a, IFNα7a and IFNα21a correspond to IFNαI, IFNαJ and IFNαF, respectively. In the instant application, these structural homologs are interferon alpha species for which modification at specified positions can be made based on 3-dimensional structural homology with IFNα-2b, IFNα2a and IFNα2c (see claim 43). Thus, contrary to the Examiner's assertions, Testa et al. does not disclose variants of IFN alpha-2b, but rather disclose mixtures of distinct naturally occurring interferon alpha species from leukocytes, not variants of IFN alpha-2b.

Analysis

As discussed above, the rejected claims are directed to *modification* of an interferon alpha species of cytokine by replacement of one or more amino acids to confer increased protease resistance compared to the unmodified interferon alpha cytokine. For a polypeptide to be within the scope of the claim, the modification must increase resistance to proteolysis, and the increase must be relative to the unmodified polypeptide. A polypeptide such as IFN-alpha 4a, which inludes, for example, an I at position 16, is not within the scope. Such polypeptide does **not** include a modification **and does not include a modification** that increases its resistance to proteolysis compared to the polypeptide without the modification. The amino acid replacement M by I at position 16 is an exemplary modification in an unmodified interferon alpha cytokine that is an **IFNα2a, IFNα2b or IFNα2c** to render the cytokine protease resistant. Replacement of M by I in any of IFNα2a, IFNα2b or IFNα2c

does not turn any of IFNα2a, IFNα2b or IFNα2c into an IFN alpha 4a nor any of the interferons that naturally contain an I at the position 16 in their sequence.

Thus, Testa *et al.* does not disclose an interferon α that (1) has one or more amino acid replacement so that it exhibits increased resistance to proteolysis; and (2) the increased resistance is compared to the unmodified interferon alpha cytokine. Furthermore, as claimed, them modification M16I as claimed **is only** with reference to interferon α-2a, -2b, or 2c. The polypeptides disclosed in Testa *et al.* is in IFN-α4a, α4b, α7a, α7b, α8a, α8b, α8c, α10a, α16, α17a, α17b, α17c, α17d, α21a and α21b. None of these interferons is an interferon α-2a, -2b, or 2c. Therefore, Testa *et al.* does not disclose a polypeptide that meets all limitations in the claims, and, thus, does not anticipate any of the claims.

III. THE REJECTION OF CLAIMS 7, 23, 341, 342, 344 and 345 UNDER 35 U.S.C. §103(a)

Claim 7, 23, 341, 342, 344 and 345 are rejected under 35 U.S.C. §103(a) as being unpatentable over Heinrichs et al. (WO 01/25438) in view of Blank et al. (Eur. J. Biochem, 265, 11-19, 1999) because Heinrichs et al. allegedly teaches interferon-alpha homolog polypeptides that are designed towards optimization for use as pharmaceuticals and to overcome dose-limiting toxicity, receptor cross-reactivity and short serum half-lives, and Blanks *et al.* teaches "possible cleavage sites for the IFN α-2b molecule" that include the E41. The Examiner concludes that it would have been obvious to have used "the methods of Heinrichs et al. to mutate the interferon α-2b at position E41 to confer the mutant increased resistance to Glu-C protease with a reasonable expectation of success." The Examiner concludes that the motivation to do so would have been suggested by Heinrichs et al., namely to improve the serum half-life and stability. This rejection respectfully is traversed.

Relevant Law

In order to set forth a prima facie case of obviousness under 35 U.S.C. § 103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be

established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Under 35 U.S.C. §103, in order to set forth a case of prima facie obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. See, *e.g.*, Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); see, also, In re Papesh, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963). In addition, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

Thus, under 35 U.S.C. §103, a claim is not patentable if either a single publication, or a combination of publications considered together, would have made the invention obvious to one of ordinary skill in the art as of the date the application is filed. For *prima facie* obviousness of a claimed invention to be established, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). This bedrock principle of U.S. law regarding obviousness was not altered by the recent Supreme Court holding in KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007). Furthermore, the Court in KSR took the opportunity to reiterate a second long-standing principle of U.S. law: that a holding of obviousness requires the fact finder (here, the Examiner), to make explicit some reason that would have led a person having ordinary skill in the art to modify a known composition in a particular manner and thereby result in the

claimed composition. Absent such a reason, the claimed composition would not have been obvious.

The Rejected Claims

Claim 7 is directed to an interferon alpha cytokine that is human and that is an IFNα-2b or an IFNα-2a or an IFNα-2C cytokine containing one or more single amino acid replacements corresponding to replacements in SEQ ID NOS:1, 182 or 185 of specified mutations, including E by Q at position 41, such that the interferon alpha cytokine has more resistance to proteolysis than the unmodified cytokine.

Claim 23 is directed to an interferon alpha-2b cytokine that comprises the sequence of amino acids set forth in any of SEQ ID NOS: 2-17, 19-131, 134-181, 978-988 or 1303, where the arginine at position 23 is replaced with a lysine. Claim 341 is directed to an interferon α-2a or -2b or 2c alpha cytokine that contains a only *single* amino acid replacement corresponding to the replacement in SEQ ID NOS: 1,182 or 185 of E by Q at position 41 and exhibits increased resistance to proteolysis compared to the unmodified interferon that does not contain the amino acid replacement.

Claim 342 is directed to an interferon alpha cytokine that contains a single amino acid replacement corresponding to the replacement in SEQ ID NOS: 1,182 or 185 of E by Q at postion 41 and exhibits increased resistance to proteolysis compared to the unmodified interferon due to replacement of a target position in the unmodified protein that increases resistance of digestion of the protein by protease.

Claim 344 is directed to is directed to an interferon alpha cytokine that contains an amino acid replacement corresponding to the replacement in SEQ ID NOS: 1,182 or 185of E by Q at position 41 and exhibits increased resistance to proteolysis compared to the unmodified interferon that does not contain the amino acid replacement.

Claim 345 is directed to an interferon alpha cytokine that has a sequence of amino acids set forth in SEQ ID NO:87.

Differences between the cited references and the claims

Heinrichs *et al.* (WO 01/25438)

Heinrichs *et al.* is directed to methods of identifying IFN-α homolog having altered properties or activities using sequence recombination, such as DNA shuffling, to produce a diverse set of recombinant nucleic acids that can be screened or selected for a desired activity. Heinrichs et al. teaches that the method can be used to select for nucleic acids having enhanced antiviral, antiproliferative, growth inhibitory, cytostatic, cytotoxic activity

or reduced immunogenicity, or other property such as low immunogenecity, increased half-life, improved solubility or oral availability. Henrichs et al. teaches IFN-α homolog that were discovered in libraries of shuffled IFN-α species from 20 human IFN-α subspecies genes. Resulting clones were assayed for antiproliferative and antiviral activity to identify those with the highest activity in *in vitro* and *in vivo* assays. Henrichs et al. also teaches that the **resulting** polypeptides can be **further** modified, for example, to increase serum half-life, reduce antigenicity, or increase polypeptide stability and teaches that such modifications include a glycosylated amino acid, a sulfated amino acid, a prenylated amino acid, an acetylated amino acid, an acylated amino acid, a PEG-ylated amino acid, a biotinylated amino acid, a carboxylated amino acid, and a phosphorylated amino acid. Thus, Henrichs *et al.* teaches a directed evolution method by which one could identify interferon mutants that have enhanced antiviral, antiproliferative, growth inhibitory, cytostatic, cytotoxic activity or reduced immunogenicity, or having other property such as low immunogenicity, increased half-life, improved solubility or oral availability.

Henrichs et al. does not teach or suggest modifying any protein to have increased resistance to any protease nor does Henrichs *et al.* teach or suggest an IFN-α homolog that exhibits increased protease resistance, nor modification of an IFN-α species or an IFN-α homolog to render it more resistant to proteases. Henrichs *et al* does not teach or suggest the modification E41Q, nor any modification specifically identified in the instant application to increase resistance to proteolysis.

Blank *et al.*

Blank *et al.* does not cure the deficiencies in the teachings of Henrichs *et al.* Blank *et al.* is directed to the identification of epitopes in IFN-α2b that confer binding to four different anti-IFNα2b monoclonal antibodies, including identification of the sequence recognized by the antibodies by comparing the immunoreactivity of various proteolytically digested fragments. To the extent Blank et al. teaches anything related to proteases, Blank et al. teaches the *possible* cleavage sites in IFN-α2b following digestion with Arg-C (C-terminal end or arginine residues), Glu-C endoprotease (C-terminal end of glutamate residues) and prolyl endopeptidases (C-terminal end or proline residues.) Specifically, Blank *et al.* teaches that *any* glutamic acid (E) is a potential cleavage site for Glu-C, *any* arginine (R) is a potential cleavage site for Arg-C and *any* proline (P) is a potential cleavage site for prolyl endopeptidases in the amino acid sequence of IFNα2b (see Figure 5). Since position 41 in the amino acid sequence of IFNα2b is Glu (E), it was identified as a ***possible*** cleavage site by

Glu-C endoprotease. Following digestion with each of the proteases, however, Blank et al. identified **actual cleavage sites** based on N-terminal sequencing of corresponding digested fragments. Glu41 is **not among** the sites identified as cleavage sites. Glu42 is identified as a cleavage site. Hence, Blank et al. cannot and does not teach protease cleavage of the IFN-α2b molecule at position 41. Notwithstanding this failure, Blank et al. does not teach or suggest any modification if any interferon, and certainly not at position 41 of any interferon α, nor any modification of any interferon, including IFN-α2b, to render it resistant to proteases. Thus, Blank *et al.* does not cure the deficiencies in the teachings of Henrichs *et al.*

The combination of teachings of Heinrich et al. with those of Blank et al. do not result in any of the instantly claimed subject matter.

Neither reference teaches or suggests (1) modifying any polypeptide to render it protease resistant; nor (2) modifying an interferon α at position 41 or at a position corresponding thereto. Thus, the combination of teachings of the two references cannot teach modification of any interferon α to render it more resistant to a proteases than the unmodified proteases, nor can the combination of teachings teach modification of an interferon α by replacing the amino acid at a position corresponding to E41 with a Q.

Specifically, combination of teachings of Heinrich et al. with those of Blank et al. fails to teach or suggest an interferon alpha cytokine that contains an amino acid replacement corresponding to E41Q, or any other amino acid replacement, conferring increased resistance of the cytokine to proteolysis compared to the unmodified cytokine not containing the mutation. There is no teaching or suggestion in either Blank et al. or Heinrich et al. that an interferon alpha cytokine can be modified to have increased protease resistance compared to the unmodified cytokine not containing the amino acid replacement. Neither reference teaches or suggest replacing E41 with Q. Therefore, the combination of teachings of Heinrichs et al. and Blank et al. does result in the instantly claimed subject matter. The Examiner has failed to set forth a *prima facie* case of obviousness.

Notwithstanding the above, the attached Declaration of Dr. Vega demonstrates results not taught or suggested by the combination of teachings of the cited references.

Notwithstanding the fact that the combination of teachings of the references fails to teach or suggest modifying a polypeptide to increase protease resistance, the combination of teachings of the reference does not teach or suggest the results achieved thereby. These results include: (1) increased resistance to protease does not require modification of all protease cleavage sites; (2) modification can be achieved without substantially altering a desired biological activity; (3) polypeptides, which are not orally available, become so upon

modification to exhibit increased protease resistance; and (4) the polypeptides modified to be exhibit increased resistance to proteases also exhibit increase serum stability and half-life.

These results are described in the application, and also demonstrated in the attached Declaration of Dr. Manuel Vega, a joint inventor, discussed below. The application, and Declaration, describe that a cytokine, including an interferon alpha cytokine, exhibiting increased resistance to proteolysis, when administered subcutaneously or orally, exhibit increased stability and half-life and thus exhibit improved pharmokinetics compared to a cytokine not containing the modification. Neither Heinrich et al. or Blank et al., singly or in combination, teaches or suggests these results.

DECLARATION

The DECLARATION of Dr. Manuel Vega provided herewith demonstrates that interferon alpha cytokines, exhibit properties not taught or suggested by the cited references nor any references of record. The DECLARATION demonstrates: (1) increased resistance to protease does not require modification of all protease cleavage sites; (2) modification can be achieved without substantially altering a desired biological activity; (3) polypeptides, which are not orally available, become so upon modification to exhibit increased protease resistance; and (4) the polypeptides modified to be exhibit increased resistance to proteases also exhibit increase serum stability and half-life.

In particular, the DECLARATION shows that modification of as few as a single residue (see Table 1), such as E41Q, results in a polypeptide that exhibits increased protease resistance. Such resistance is not necessarily resistance to a particular protease, but to a variety of proteases. The DECLARATION demonstrates that when modified based on the property of increased protease resistance, exhibit increased resistance to proteases *in vitro* and *in vivo*. For example, as described in the application and as provided in the DECLARATION, exemplary candidate LEAD polypeptides tested for proteolysis against a cocktail of proteases *in vitro* exhibited increased proteolysis compared to an IFNα-2b not containing the modification.

The DECLARATION also demonstratest that the resulting modified cytokines can retain original activity. As described in the DECLARATION, the results show that the exemplary mutant E41Q in IFNα2b not only exhibits increased protease resistance to a cocktail of proteases, but also to blood lysate, serum and to chymotrypsin. Thus, the amino acid replacement confers increased protease resistance of the cytokine across the entire molecule, which increased resistance is not specific to a particular protease.

In the DECLARATION, data also are provided to demonstrate that the proteins exhibit improved pharmacokinetics upon subcutaneous and oral administration compared to proteins not containing the amino acid replacement(s). For example, the DECLARATION provides data demonstrating that a mutant IFN-α containing only a single amino acid mutation (E41Q), when administered subcutaneously or orally, retains anti-viral activity in the serum for a longer time period than the native polypeptide. In addition, the result show that SuperLEADs, containing two or more amino acid changes described in the above-captioned application, also exhibit similar increases in half-life. Thus, an IFN-α, containing in many instances only a single amino acid replacement to render the cytokine protease resistance, can be used as a therapeutic due to the improved properties compared to the native polypeptide.

In the case of per-oral administration, the native polypeptide retains **no** detectable activity when administered; whereas, the IFN-α with a single amino acid change, can be successfully administered orally. For example, Figure 3 shows that unmodified interferon alpha cannot be adminstered orally; whereas, a modified form, with only a single a amino acid change can be administered orally and exhibit anti-viral activity in the serum. This really is astounding, and of enormous medical and economic value. Therefore, the results provided in the DECLARATION show that the interferon alpha cytokines as claimed have properties that are not taught or suggested by any of the cited references.

None of the cited references, singly or in any combination thereof, teaches or suggest modifying the cytokine by amino acid replacement(s) to render the molecule resistant to proteases, nor teaches any of the modifications described in the application, including E41Q. None teaches or suggests that a polypeptide having increased protease resistance would exhibit increased half-life and stability upon subcutaneous or per-oral administration. None of the cited references, singly or in any combination, teaches or suggests that modification to render a polypeptide protease resistant, renders a polypeptide, that had not been orally available, suitable oral administration. Therefore, the claims cannot be obvious in view of the cited references.

Furthermore, to combine these references to result in the instant claims relies on the improper use of hindsight

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the

inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The Examiner urges that it would have been obvious to use the methods of Heinrichs et al. to mutate IFNα2b at position E41 to confer the mutant with increased protease resistance, and to do so would have been suggested by Heinrichs et al. to improve serum half-life and stability. Notwithstanding the fact that the combination of references do not lead to the instant claims, there is no teaching or suggestion in any of Heinrichs et al. or Blank et al. that modifying a protease cleavage site would render the entire molecule resistant to proteolysis compared to the cytokine not containing the modification, and that such increased resistance to proteolysis would confer increased half-life and stability. To reach this conclusion, the Examiner states, that the motivation to increase resistance to a protease, Glu-C, is found in the teachings of Henrichs *et al.* to modify polypeptides to increase serum half-life and stability. Neither reference, however, teaches or suggests that modification of a polypeptide to exhibit increased resistance to a protease leads to an increase in serum half-life or stability. It is the instant application that teaches this link; it is the instant application that teaches rendering a polypeptide, such as an interferon α more resistant to proteases increases half-life or stability. Thus, the Examiner has combined the teachings of the cited references with the teachings of the application. Therefore, the Examiner improperly relies on hindsight.

Furthermore, as discussed above, the increased resistance of the entire molecule to proteolysis can be achieved by modifications of only a few residues, and in many instances by only a single amino acid change. Neither cited reference teaches or suggests that protease resistance or any property can be modified by changing only a few residues. Blank *et al.* identifies **four or five** protease cleavage sites. Nowhere in either Blank *et al.* or Henrichs *et al.* is there a teaching or suggestion that modification of fewer than all of the sites will increase resistance of the entire polypeptide to protease cleavage.

Therefore, for any and all of these reasons, the Examiner has failed to set forth a *prima facie* case of obviousness. Applicant respectfully requests reconsideration of this rejection.

* * *

In view of the above, examination of the application on the merits and allowance are respectfully requested.

Respectfully submitted,

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CLUSTAL W (1.83) multiple sequence alignment

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SEQIDNO193 (H)          CNLSQTHSLNNRRTLMLMAQMRRISPFSCLKDRHDFEFPQEEFDGNQFQKAQAISVLHEM 60
SEQIDNO195 (8)          CDLPQTHSLGNRRALILLAQMRRISPFSCLKDRHDFEFPQEEFDDKQFQKAQAISVLHEM 60
SEQIDNO183 (c)          CDLPQTHSLGNRRALILLGQMGRISPFSCLKDRHDFRIPQEEFDGNQFQKAQAISVLHEM 60
SEQIDNO191 (I)          CDLPQTHSLGNRRALILLAQMGRISPFSCLKDRHDFGLPQEEFDGNQFQKTQAISVLHEM 60
SEQIDNO189 (4)          CDLPQTHSLGNRRALILLAQMGRISHFSCLKDRHDFGFPEEEFDGHQFQKAQAISVLHEM 60
SEQIDNO190 (4b)         CDLPQTHSLGNRRALILLAQMGRISHFSCLKDRHDFGFPEEEFDGHQFQKTQAISVLHEM 60
SEQIDNO192 (J)          CDLPQTHSLRNRRALILLAQMGRISPFSCLKDRHEFRFPEEEFDGHQFQKTQAISVLHEM 60
SEQIDNO194 (F)          CDLPQTHSLGNRRALILLAQMGRISPFSCLKDRHDFGFPQEEFDGNQFQKAQAISVLHEM 60
SEQIDNO232 (con)        CDLPQTHSLGNRRALILLAQMRRISPFSCLKDRHDFG-PQEEFDGNQFQKAQAISVLHEM 59
SEQIDNO182 (2a)         CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEF-GNQFQKAETIPVLHEM 59
SEQIDNO185 (2c)         CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRRDFGFPQEEF-GNQFQKAETIPVLHEM 59
SEQIDNO1   (2b)         [redacted]                                                    59
SEQIDNO188 (6)          CDLPQTHSLGHRRTMMLLAQMRRISLFSCLKDRHDFRFPQEEFDGNQFQKAEAISVLHEV 60
SEQIDNO186 (d)          CDLPETHSLDNRRTLMLLAQMSRISPSSCLMDRHDFGFPQEEFDGNQFQKAPAISVLHEL 60
SEQIDNO187 (5)          CDLPQTHSLSNRRTLMIMAQMGRISPFSCLKDRHDFGFPQEEFDGNQFQKAQAISVLHEM 60
                        *:*.:****  **::::::.** :**  *** **::*  *:*** .:****: :*.****:

SEQIDNO193 (H)    MQQTFNLFSTKNSSAAWDETLLEKFYIELFQQMNDLEACVIQEVGVEETPLMNEDSILAV 120
SEQIDNO195 (8)    IQQTFNLFSTKDSSAALDETLLDEFYIELDQQLNDLESCVMQEVGVIESPLMYEDSILAV 120
SEQIDNO183 (c)    IQQTFNLFSTEDSSAAWEQSLLEKFSTELYQQLNDLEACVIQEVGVEETPLMNEDSILAV 120
SEQIDNO191 (I)    IQQTFNLFSTEDSSAAWEQSLLEKFSTELYQQLNNLEACVIQEVGMEETPLMNEDSILAV 120
SEQIDNO189 (4)    IQQTFNLFSTEDSSAAWEQSLLEKFSTELYQQLNDLEACVIQEVGVEETPLMNEDSILAV 120
SEQIDNO190 (4b)   IQQTFNLFSTEDSSAAWEQSLLEKFSTELYQQLNDLEACVIQEVGVEETPLMNVDSILAV 120
SEQIDNO192 (J)    IQQTFNLFSTEDSSAAWEQSLLEKFSTELYQQLNDLEACVIQEVGVEETPLMNEDFILAV 120
SEQIDNO194 (F)    IQQTFNLFSTKDSSATWEQSLLEKFSTELNQQLNDLEACVIQEVGVEETPLMNVDSILAV 120
SEQIDNO232 (con)  IQQTFNLFSTKDSSAAWDESLLEKFYTELYQQLNDLEACVIQEVGVEETPLMNVDSILAV 119
SEQIDNO182 (2a)   IQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAV 119
SEQIDNO185 (2c)   IQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAV 119
SEQIDNO1   (2b)   [redacted]                                                    119
SEQIDNO188 (6)    IQQTFNLFSTKDSSVAWDERLLDKLYTELYQQLNDLEACVMQEVWVGGTPLMNEDSILAV 120
SEQIDNO_186(d)    IQQIFNLFTTKDSSAAWDEDLLDKFCTELYQQLNDLEACVMQEERVGETPLMNADSILAV 120
SEQIDNO187 (5)    IQQTFNLFSTKDSSATWDETLLDKFYTELYQQLNDLEACMMQEVGVEDTPLMNVDSILTV 120
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SEQIDNO193 (H)    KKYFQRITLYLMEKKYSPCAWEVVRAEIMRSLSFSTNLQKRLRRKD 166
SEQIDNO195 (8)    RKYFQRITLYLTEKKYSSCAWEVVRAEIMRSFSLSINLQKRLKSKE 166
SEQIDNO183 (c)    RKYFQRITLYLIERKYSPCAWEVVRAEIMRSLSFSTNLQKRLRRKD 166
SEQIDNO191 (I)    RKYFQRITLYLTEKKYSPCAWEVVRAEIMRSLSFSTNLQKILRRKD 166
SEQIDNO189 (4)    RKYFQRITLYLTEKKYSPCAWEVVRAEIMRSLSFSTNLQKRLRRKD 166
SEQIDNO190 (4b)   RKYFQRITLYLTEKKYSPCAWEVVRAEIMRSLSFSTNLQKRLRRKD 166
SEQIDNO192 (J)    RKYFQRITLYLMEKKYSPCAWEVVRAEIMRSFSFSTNLKKGLRRKD 166
SEQIDNO194 (F)    KKYFQRITLYLTEKKYSPCAWEVVRAEIMRSFSLSKIFQERLRRKE 166
SEQIDNO232 (con)  KKYFQRITLYLTEKKYSPCAWEVVRAEIMRSFSLSTNLQERLRRKE 165
SEQIDNO182 (2a)   RKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKE 165
SEQIDNO185 (2c)   RKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKE 165
SEQIDNO1   (2b)   [redacted]                                      165
SEQIDNO188 (6)    RKYFQRITLYLTEKKYSPCAWEVVRAEIMRSFSSSRNLQERLRRKE 166
SEQIDNO_186(d)    KKYFRRITLYLTEKKYSPCAWEVVRAEIMRSLSLSTNLQERLRRKE 166
SEQIDNO187 (5)    RKYFQRITLYLTEKKYSPCAWEVVRAEIMRSFSLSANLQERLRRKE 166
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